TRACING CO-REGULATORY NETWORK DYNAMICS IN NOISY, SINGLE-CELL TRANSCRIPTOME TRAJECTORIES.

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Public Summary:
In this paper we describe a new method called SCIMITAR for inferring "trajectories" of progressing cells from single cell RNA-Seq data. The method uses gaussian mixtures that smoothly change over the inferred transitions. A huge advantage of the method is that gene expression modules can be identified that reveal the regulatory underpinnings of the cellular transformation mechanism.

Scientific Abstract:
The availability of gene expression data at the single cell level makes it possible to probe the molecular underpinnings of complex biological processes such as differentiation and oncogenesis. Promising new methods have emerged for reconstructing a progression 'trajectory' from static single-cell transcriptome measurements. However, it remains unclear how to adequately model the appreciable level of noise in these data to elucidate gene regulatory network rewiring. Here, we present a framework called Single Cell Inference of MorphIng Trajectories and their Associated Regulation (SCIMITAR) that infers progressions from static single-cell transcriptomes by employing a continuous parametrization of Gaussian mixtures in high-dimensional curves. SCIMITAR yields rich models from the data that highlight genes with expression and co-expression patterns that are associated with the inferred progression. Further, SCIMITAR extracts regulatory states from the implicated trajectory-evolvingco-expression networks. We benchmark the method on simulated data to show that it yields accurate cell ordering and gene network inferences. Applied to the interpretation of a single-cell human fetal neuron dataset, SCIMITAR finds progression-associated genes in cornerstone neural differentiation pathways missed by standard differential expression tests. Finally, by leveraging the rewiring of gene-gene co-expression relations across the progression, the method reveals the rise and fall of co-regulatory states and trajectory-dependent gene modules. These analyses implicate new transcription factors in neural differentiation including putative co-factors for the multi-functional NFAT pathway.